*Acta Medica Okayama*

*Volume* 64, *Issue* 3 2010 *Article* 7

JUNE 2010

# Relationship between Estimated Glomerular Filtration Rate (eGFR) and Metabolic Syndrome in Japanese

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## Abstract

We investigated the link between renal function as evaluated by estimated glomerular filtration rate (eGFR) and metabolic syndrome in Japanese. A total of 11,711 Japanese subjects, aged 20-79 years, were recruited in a cross-sectional clinical investigation. From this group, we further investigated the data on 1,576 subjects. eGFR was calculated using serum creatinine (Cr), age and sex. The diagnosis of metabolic syndrome was based on the Japanese criteria. In the first analysis, 288 men (7.8%) and 498 women (6.2%) were diagnosed with reduced eGFR ($<$60ml/min). eGFR was not correlated with anthropometric, body composition parameters in either sex. In the second analysis, in subjects without medications, 132 men (20.8%) and 15 women (1.6%) were diagnosed with metabolic syndrome. eGFR was lower in men with abdominal obesity and in women with hypertension was than in those without. Among Japanese not taking medications, lower eGFR may be a characteristic of men with abdominal obesity and of women with hypertension.

**KEYWORDS:** metabolic syndrome, estimated glomerular filtration rate (eGFR), abdominal circumference

Acta Med. Okayama, 2010
Vol. 64, No. 3, pp. 203-208


Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

*Original Article*

# Relationship between Estimated Glomerular Filtration Rate (eGFR) and Metabolic Syndrome in Japanese

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**We investigated the link between renal function as evaluated by estimated glomerular filtration rate (eGFR) and metabolic syndrome in Japanese. A total of 11,711 Japanese subjects, aged 20-79 years, were recruited in a cross-sectional clinical investigation. From this group, we further investigated the data on 1,576 subjects. eGFR was calculated using serum creatinine (Cr), age and sex. The diagnosis of metabolic syndrome was based on the Japanese criteria. In the first analysis, 288 men (7.8%) and 498 women (6.2%) were diagnosed with reduced eGFR (<60 ml/min). eGFR was not correlated with anthropometric, body composition parameters in either sex. In the second analysis, in subjects without medications, 132 men (20.8%) and 15 women (1.6%) were diagnosed with metabolic syndrome. eGFR was lower in men with abdominal obesity and in women with hypertension was than in those without. Among Japanese not taking medications, lower eGFR may be a characteristic of men with abdominal obesity and of women with hypertension.**

**Key words:** metabolic syndrome, estimated glomerular filtration rate (eGFR), abdominal circumference

Chronic kidney disease (CKD) has become an important public health challenge in Japan and is a major risk factor for end-stage renal disease, cardiovascular disease and premature death [1, 2]. Identifying and treating risk factors for early chronic kidney disease may be the best approach to preventing and delaying adverse outcomes [1]. In Japan, clinical practice guidelines established by the Japanese Society of Nephrology estimate that 18.7% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) $<60$ ml/min/1.73m$^2$ for at least 3 months regardless of cause [3], and that 4.1% have moderate or severe CKD [4].

Metabolic syndrome is characterized by abdominal obesity, high blood pressure, dyslipidemia and impaired glucose tolerance [5]. In Japan, according to the criteria for this syndrome as defined in April 2005, 30.7% of men and 3.6% of women have metabolic syndrome [6, 7]. In some studies, CKD is closely related to body composition parameters and metabolic syndrome [8-18]. However, the link between renal function evaluated by estimated GFR (eGFR) and metabolic syndrome components using the Japanese criteria remains to be investigated.

In this study, we investigated renal function evaluated by eGFR in Japanese and evaluated the clinical impact of metabolic syndrome on eGFR in subjects not taking medications.

Received November 2, 2009; accepted February 4, 2010.
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## Subjects and Methods

***Subjects.*** In the first analysis, we used all data on 11,711 Japanese (3,674 men and 8,037 women) aged 20–79 years in a cross-sectional study. All subjects met the following criteria: (1) they had been wanting to change their lifestyle *i.e.*, diet and exercise habits, and had received an annual health checkup from June 1997 to May 2007 at Okayama Southern Institute of Health; (2) their creatinine (Cr) and anthropometric measurements had been taken as part of their annual health checkups; and (3) they provided informed consent (Table 1).

In the second analysis, among the 11,711 subjects, we further examined the data on 1,576 subjects (636 men and 940 women) who undertook fasting blood examination and blood pressure measurements and who were currently taking no medications; we also examined the Cr and anthropometric measurements of these second-analysis subjects (Table 2). In addition, medical staff subjectively evaluated these subjects' lifestyles, and encouraged subjects with fasting plasma glucose $\geqq 126$ mg/dl to begin taking medication.

The study was approved by the Ethics Committee

Table 1 Clinical profiles of subjects in the first analysis

| | Men (n = 3,674) | | | Women (n = 8,037) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Minimum | Maximum | Mean ± SD | Minimum | Maximum |
| Age | 43.8 ± 14.2 | 20 | 79 | 42.9 ± 14.1 | 20 | 79 |
| Height (cm) | 168.9 ± 6.2 | 143.7 | 187.6 | 156.2 ± 5.7 | 134.9 | 179.3 |
| Body weight (kg) | 70.3 ± 11.7 | 39.1 | 175.7 | 55.1 ± 9.0 | 32.1 | 116.9 |
| BMI (kg/m$^2$) | 24.6 ± 3.7 | 13.6 | 61.5 | 22.6 ± 3.6 | 12.9 | 48.7 |
| Body fat percentage (%) | 24.3 ± 6.7 | 1.2 | 47.9 | 30.7 ± 7.0 | 3.9 | 56.2 |
| Abdominal circumference (cm) | 84.3 ± 10.2 | 58.0 | 157.0 | 72.3 ± 9.7 | 43.3 | 123.6 |
| Hip circumference (cm) | 94.2 ± 6.3 | 71.0 | 145.5 | 91.0 ± 6.0 | 58.5 | 132.0 |
| Cr (mg/dl) | 0.83 ± 0.15 | 0.39 | 2.57 | 0.61 ± 0.21 | 0.20 | 8.63 |
| eGFR (ml/min/1.73m$^2$) | 84.8 ± 18.7 | 20.2 | 191.3 | 90.6 ± 22.7 | 4.3 | 260.0 |

BMI: body mass index
Cr: creatinine
eGFR: estimated glomerular filtration rate

Table 2 Clinical profiles of subjects in the second analysis

| | Men (n = 636) | | | Women (n = 940) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Minimum | Maximum | Mean ± SD | Minimum | Maximum |
| Age | 43.8 ± 11.2 | 20 | 78 | 45.7 ± 11.6 | 20 | 76 |
| Height (cm) | 169.1 ± 6.0 | 146.9 | 187.6 | 156.7 ± 5.5 | 139.3 | 176.3 |
| Body weight (kg) | 71.5 ± 11.2 | 40.1 | 121.7 | 56.0 ± 8.9 | 37.1 | 105.3 |
| BMI (kg/m$^2$) | 25 ± 3.5 | 16.4 | 43.3 | 22.8 ± 3.5 | 15.7 | 41.3 |
| Body fat percentage (%) | 24.4 ± 6.3 | 2.2 | 41.3 | 31.1 ± 6.6 | 10.6 | 50.1 |
| Abdominal circumference (cm) | 84.7 ± 9.5 | 58.8 | 123.0 | 72.5 ± 9.0 | 55.5 | 115.6 |
| Hip circumference (cm) | 94.9 ± 5.8 | 79.1 | 121.0 | 91.3 ± 6.1 | 60.0 | 122.0 |
| Cr (mg/dl) | 0.83 ± 0.14 | 0.50 | 1.85 | 0.62 ± 0.12 | 0.36 | 1.10 |
| eGFR (ml/min/1.73m$^2$) | 84.0 ± 16.8 | 36.0 | 146.5 | 84.5 ± 18.7 | 38.3 | 166.8 |
| Systolic blood pressure (mmHg) | 129.6 ± 15.7 | 90.0 | 205.0 | 121.3 ± 16.4 | 88.0 | 193.0 |
| Diastolic blood pressure (mmHg) | 81.2 ± 11.1 | 33.0 | 131.0 | 75.2 ± 10.2 | 44.0 | 120.0 |
| Triglyceride (mg/dl) | 142.5 ± 116.8 | 29.0 | 1,683.0 | 93.6 ± 14.7 | 70.0 | 331.0 |
| HDL cholesterol (mg/dl) | 55.4 ± 14.6 | 18.0 | 120.0 | 67.2 ± 16.4 | 28.0 | 151.0 |
| Blood sugar (mg/dl) | 100.6 ± 16.8 | 63.0 | 218.0 | 93.6 ± 14.7 | 70.0 | 331.0 |

BMI: body mass index
Cr: creatinine
eGFR: estimated glomerular filtration rate

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***Anthropometric and body composition measurements.*** The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]$^2$ (kg/m$^2$). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration [19]. Body fat percentage was measured by an air displacement plethysmograph called the BOD POD Body Composition System (Life Measurement Instruments, Concord, CA, USA) [20, 21].

***Blood pressure measurements.*** Each participant's blood pressure was measured after resting at least 15 min in the sitting position.

***Blood sampling and assays.*** The level of Cr was measured with an automated biochemical analyzer (model 7700; HITACHI, Tokyo, Japan) and Accuras Auto CRE (Shino-Test Corporation, Tokyo, Japan). High-density lipoprotein (HDL) cholesterol [22], triglycerides (L Type Wako Triglyceride・H, Wako Chemical, Osaka, Japan) and plasma glucose (hexokinase method) were also measured at the Okayama Southern Institute of Health, Okayama Health Foundation. The accuracy of the measurements was maintained during the study period. eGFR was calculated using the following equation: eGFR (ml/min/1.73 m$^2$) $= 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287}$ (for men) and eGFR (ml/min/1.73 m$^2$) $= 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287} \times 0.739$ (for women) [23]. Reduced eGFR was defined as an eGFR $< 60$ ml/min/1.73 m$^2$.

***Definition of metabolic syndrome.*** The syndrome was defined [6], among men with an abdominal circumference in excess of 85 cm and women with an abdominal circumference in excess of 90 cm [24], as having 2 or more of the following components: 1) dyslipidemia: triglyceride $\geq 150$ mg/dl and/or HDL cholesterol $< 40$ mg/dl; 2) hypertension: blood pressure $\geq 130/85$ mmHg; 3) Impaired glucose tolerance: fasting plasma glucose $\geq 110$ mg/dl.

***Statistical analysis.*** Data are expressed as means $\pm$ standard deviation (SD) values. A comparison of parameters between the 2 groups was made using the unpaired *t*-test and covariance analysis. Simple correlation analysis was performed as well to test for the significance of the linear relationship among continuous variables: $p < 0.05$ was considered statistically significant. Statistical analysis was performed with StatView 5.0 (SAS Institute Inc., Cary, NC, USA).

## Results

In the first analysis, the mean eGFR was $84.8 \pm 18.7$ ml/min/1.73 m$^2$ in men and $90.6 \pm 22.7$ ml/min/1.73 m$^2$ in women (Table 1). A diagnosis of reduced eGFR was made for 288 men (7.8%) and 498 women (6.2%). eGFR was not clearly correlated with anthropometric, body composition parameters in either sex (Table 3). eGFR in men with abdominal obesity ($81.8 \pm 17.8$ ml/min/1.73 m$^2$) was lower than that in men without abdominal obesity ($87.4 \pm 19.1$ ml/min/1.73 m$^2$), but the difference was not significant after adjusting for age ($p = 0.0675$). eGFR in women with abdominal obesity ($83.8 \pm 22.2$ ml/min/1.73 m$^2$) was similar to that in women without abdominal obesity after adjusting for age ($91.0 \pm 22.6$ ml/min/1.73 m$^2$) ($p = 0.8039$).

In the second analysis, we clarified the prevalence of metabolic syndrome among subjects who were not taking without medications (Table 4). Among the 1,576 Japanese subjects, 306 men (48.1%) had an abdominal circumference in excess of 85 cm and 48 women (5.1%) had an abdominal circumference

Table 3 Relationship between eGFR and anthropometric, body composition parameters

| | Men | | Women | |
|---|---|---|---|---|
| | r | *p* | r | *p* |
| Body weight (kg) | −0.017 | 0.2929 | −0.110 | <0.0001 |
| BMI (kg/m$^2$) | −0.086 | <0.0001 | −0.174 | <0.0001 |
| Body fat percentage (%) | −0.146 | <0.0001 | −0.205 | <0.0001 |
| Abdominal circumference | −0.142 | <0.0001 | −0.233 | <0.0001 |
| Hip circumference (cm) | −0.006 | 0.7210 | −0.060 | <0.0001 |

Table 4 Comparison of eGFR between subjects with and without metabolic syndrome

| **Men** | Abdominal obesity (+) | Abdominal obesity (−) | *p* | *p* (Afrer adjusting for age) |
|---|---|---|---|---|
| Number of subjects | 306 | 330 | | |
| eGFR (ml/min/1.73 m$^2$) | 83.8 ± 14.9 | 84.1 ± 18.4 | 0.7865 | 0.0055 |
| | Impaired glucose torelance (+) | Impaired glucose torelance (−) | | |
| Number of subjects | 104 | 532 | | |
| eGFR (ml/min/1.73 m$^2$) | 86.9 ± 16.4 | 83.4 ± 16.8 | 0.0479 | 0.0880 |
| | Hypertension (+) | Hypertension (−) | | |
| Number of subjects | 347 | 289 | | |
| eGFR (ml/min/1.73 m$^2$) | 82.7 ± 16.0 | 85.5 ± 17.6 | 0.0338 | 0.1106 |
| | Dyslipidemia (+) | Dyslipidemia (−) | | |
| Number of subjects | 223 | 413 | | |
| eGFR (ml/min/1.73 m$^2$) | 83.1 ± 16.6 | 84.4 ± 16.9 | 0.3501 | 0.6986 |
| | **Metabolic syndrome (+)** | **Metabolic syndrome (−)** | | |
| Number of subjects | 132 | 504 | | |
| eGFR (ml/min/1.73 m$^2$) | 83.6 ± 15.7 | 84.1 ± 17.1 | 0.7632 | 0.0830 |
| **Women** | Abdominal obesity (+) | Abdominal obesity (−) | | |
| Number of subjects | 48 | 892 | | |
| eGFR (ml/min/1.73 m$^2$) | 84.8 ± 16.7 | 84.5 ± 18.8 | 0.9179 | 0.2654 |
| | Impaired glucose torelance (+) | Impaired glucose torelance (−) | | |
| Number of subjects | 50 | 890 | | |
| eGFR (ml/min/1.73 m$^2$) | 86.0 ± 18.1 | 84.4 ± 18.8 | 0.5651 | 0.8745 |
| | Hypertension (+) | Hypertension (−) | | |
| Number of subjects | 300 | 640 | | |
| eGFR (ml/min/1.73 m$^2$) | 80.6 ± 17.0 | 86.3 ± 19.3 | <0.0001 | 0.0222 |
| | Dyslipidemia (+) | Dyslipidemia (−) | | |
| Number of subjects | 108 | 832 | | |
| eGFR (ml/min/1.73 m$^2$) | 80.6 ± 20.0 | 85.0 ± 18.5 | 0.0223 | 0.2757 |
| | **Metabolic syndrome (+)** | **Metabolic syndrome (−)** | | |
| Number of subjects | 15 | 925 | | |
| eGFR (ml/min/1.73 m$^2$) | 81.5 ± 17.0 | 84.6 ± 18.8 | 0.5297 | 0.1077 |

Mean ± SD

exceeding 90 cm. In addition, 132 men (20.8%) and only 15 women (1.6%) were diagnosed with the syndrome.

In subjects not taking medications, we also compared eGFR levels between the groups with and without each component of the Japanese definition of metabolic syndrome (Table 4). To avoid the influence of age, we used age as a covariate and compared eGFR between Japanese with and those without metabolic syndrome components using covariance analysis. eGFR in men with abdominal obesity and in women with hypertension was significantly lower than in subjects without these components of metabolic syndrome, even after adjusting for age. However, there were no significant differences in eGFR between the groups with or without other components of metabolic syndrome. In addition, eGFR in subjects with metabolic syndrome was similar to that in subjects without it, even after adjusting for age.

## Discussion

Obesity is a significant risk factor for developing CKD and proteinuria [8–11]. Fox *et al.* reported that the odds ratio (OR) for developing new-onset kidney disease, defined as a GFR $< 59.3$ ml/min/1.73 m$^2$ in

women and 64.3 ml/min/$m^2$ in men, was 1.23, representing a 23% increase in BMI within 10 -years [8]. In Japan, it was also reported that BMI above 25 kg/$m^2$ was linked to proteinuria [9]. Bonnet *et al.* reported that abdominal obesity was related to the development of elevated albuminuria in both sexes, suggesting that the measurement of abdominal circumference might improve the identification of non-diabetic individuals at risk of developing microalbuminuria [10]. In addition, a greater waist-to-hip ratio was associated with a greater risk for diminished filtration, even when corrected for BMI [11]. In this study, the relationships between eGFR and anthropometric, body composition parameters were not clearly revealed in the first analysis. However, after adjusting for age by using covariance analysis, eGFR in men with abdominal obesity tended to be lower than that in men without abdominal obesity in the first and second analyses. Therefore, we could not accurately prove a link between eGFR and anthropometric, body composition parameters, unlike the case in previous studies.

This study is the first to reveal a relationship between eGFR and metabolic syndrome, defined by the new Japanese criteria of metabolic sundrome. Metabolic syndrome has important clinical and public health implications in Japan because it is a common disorder in that country [7]. Previous studies have documented that metabolic syndrome is an important risk factor for diabetes, coronary heart disease and stroke [25–27]. The present study shows new and important information about the relationship between eGFR and metabolic syndrome in a large sample of Japanese.

Subjects with metabolic syndrome, using the modified Adult Treatment Panel (ATP) III definition [28], showed higher urinary albumin excretion and left ventricular mass index, increased intima-media thickness, and a higher prevalence of microalbuminuria [12]. Compared with subjects with 0 or 1 component of the metabolic syndrome, subjects with 2, 3, 4, or 5 components of the syndrome had multivariate-adjusted odds ratios of 2.21, 3.38, 4.23, and 5.85 for CKD [13]. Using the Japanese criteria, we previously reported that the prevalence of proteinuria in subjects with metabolic syndrome was significantly higher than that in subjects without the syndrome [14]. Tanaka *et al.* [15], Ninomiya T *et al.* [16] and Iseki *et al.* [17] reported that metabolic syndrome, using the modified ATP III definition, was associated with CKD in Japanese. Although Tsuda *et al.* [18] revealed that the level of microalbuminuria in subjects with metabolic syndrome according to the Japanese criteria was significantly higher than that in subjects without the syndrome, the link between eGFR and metabolic syndrome using the Japanese criteria has not been investigated until now. In this study, although we evaluated eGFR in subjects without medications, the clinical impact of abdominal obesity in men and hypertension in women was noted in the second analysis. However, eGFR in subjects with metabolic syndrome was similar to that in subjects without the syndrome in either sex. eGFR was higher in subjects with impaired glucose tolerance than in those without, but not significantly. Glomerular hyperfiltration exists among Japanese type 2 diabetic patients with no evidence of overt proteinuria or hypertension [29]. In addition, according to the analysis of subjects without medications, the link between eGFR and metabolic syndrome and its components may be attenuated. Therefore, a significant difference in eGFR between subjects with and without metabolic syndrome might not be noted.

Potential limitations remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, the 11,711 subjects, all of whom wanted to change their lifestyle, underwent measurements for this study: they were therefore more health-conscious than the average person. The selected 1,576 subjects underwent fasting blood examination and blood pressure measurements and were taking no medications; they were therefore more health-conscious than most of the subjects in the first analysis. Although some subjects were within the range of fasting plasma glucose levels at wthich medications are recommended, the prevalence of metabolic syndrome in this study was lower than in our previous report [7]. This was especially true in women, only 15 of whom were diagnosed as having metabolic syndrome. The small sample size in women with metabolic syndrome might make it difficult to compare eGFR between women with the syndrome and those without. Third, we could not accurately prove the mechanism between lower eGFR and metabolic syndrome components. Further prospective studies are needed in Japanese subjects using the new Japanese criteria.

Acknowledgments. This research was supported in part by Research

Grants from the Ministry of Health, Labor, and Welfare, Japan.

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